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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,650	LEVINE ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 28-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 28-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the communication filed 1/19/05. It is acknowledged that the previous Examiner indicated allowable claims, and suspended the case due to a potential interference. However, upon further review, the pending claims are not allowable for the reasons set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 28-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide

sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof.

The instant claims encompass a genus of chimeric molecules that includes protein molecules as well as molecules comprising non-protein components. Furthermore, the claims encompass a genus of molecules comprising a genus of "targeting peptides" that specifically bind to a vascular endothelium (e.g., see claim 1). It is note that the claims are very broad and, given the broadest reasonable interpretation, encompass all possible "targeting peptides" that target any vascular endothelium. Therefore, the claims encompass possibly hundreds of thousands to millions of different molecules and targeting peptides including peptides that are unrelated in structure and which have different binding specificities (i.e., different functions), including peptides that have yet to be identified and/or made.

In this case, the specification has only disclosed chimeric molecules that are chimeric polypeptide molecules. Furthermore, the only targeting peptides described in the specification are the 5 specific peptides disclosed as SEQ ID NOS: 1-5 which are disclosed as specifically binding cardiac vasculature. However, there is no disclosure identifying any structural elements common to the genus of molecules, nor is there an identification of any structure/function relationship common to the members of the genus. The only disclosed commonality is the ability of the targeting peptides to specifically bind to a cardiac vasculature. Therefore, the specification has only disclosed a functional relationship between the members of the genus and has identified 5 specific peptides. It is noted that the five disclosed targeting peptides (SEQ ID NOS: 1-5) do not appear to have any structural relationship. Accordingly, in the absence of

sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of targeting peptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only chimeric molecules that are chimeric polypeptide molecules comprising the targeting peptides set forth in SEQ ID NOS: 1-5 which specifically bind to cardiac vasculature, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-7 and 28-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a product such as:

> A chimeric polypeptide comprising an angiogenic factor wherein that is covalently linked to a targeting peptide wherein said targeting peptide comprises SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5; and wherein said targeting peptide specifically binds to cardiac vascular endothelium;

does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The instant claims are drawn to a genus of chimeric molecules comprising an angiogenic factor and a targeting peptide that specifically binds to a vascular endothelium. The specification indicates that the chimeric molecules are useful for treating vascular diseases. Therefore, the nature of the invention is therapeutic molecule.

The claims are very broad. For instance, the claims encompass a genus of chimeric molecules comprising "targeting peptides" that include possibly thousands of different peptide molecules, including molecules that are structurally unrelated and molecules that have yet to be identified and/or made. Furthermore the claims are very broad with respect to the site that the peptides specifically bind. For instance, the claims encompass targeting peptides that

specifically bind to a vascular endothelium (i.e., any vascular endothelium). It is noted that "vascular endothelium" encompass all vasculature endothelia including endothelium cardiac and peripheral vascular endothelium such as the vascular endothelium found in the limbs and organs other than the heart (e.g., see p. 26, lines 28-31 of the specification).

The specification has disclosed that five specific targeting peptides (SEQ ID NO: 1-5) have been identified. The specification discloses that four of the five targeting peptides specifically bind to cardiac vasculature (SEQ ID NOS: 1-4) while one of the disclosed targeting peptides (SEQ ID NO: 5) specifically binds to ischemic myocardium (e.g., see p. 27 of the specification). The specification does not disclose any targeting peptides that specifically bind to a vascular endothelium other than cardiac vascular endothelium. Furthermore, the specification has only disclosed chimeric polypeptide molecules, and has not disclosed any chimeric molecules that comprise non-peptide components.

The prior art does not teach a chimeric molecule comprising a peptide angiogenic factor and a targeting moiety that specifically binds to a vascular endothelium. The specification does not indicate that any of the identified targeting peptides (i.e., SEQ ID NO: 1-5) specifically bind to any other vascular endothelium other than cardiac vasculature. As indicated below, the art does teach a chimeric molecule that targets vascular endothelium wherein the chimeric molecule comprises a targeting peptide and an antiangiogenic factor, such as doxorubicin (see below).

Furthermore, the prior art recognizes that not all vasculature endothelium is the same. For instance, Rajotte et al. (J Clin. Invest., 1998; previously cited) studied the molecular heterogeneity of the vascular endothelium using the phage display method and reported that there is not only heterogeneity of the endothelium between tissues, but even within a given

tissue. For example, in lungs, ligands GFE-I and GFE-2 stained mainly capillaries compared to larger vessels (page 436 col 1). Thus, the peptides that target vasculature endothelium are unlikely to target all vasculature endothelium in general; rather it is more likely that the targeting peptides target specific vasculature endothelium. This is consistent with the instant disclosure which indicates four targeting peptides that specifically bind to normal cardiac vasculature and one that specifically binds to ischemic cardiac vasculature.

Therefore, additional experimentation would be required for one of skill in the art to be able to make and/or use the instant claimed invention to its full scope. Specifically, additional experimentation would be required with respect to the described targeting peptides that specifically bind to vascular endothelium other than cardiac vasculature. Since the only targeting polypeptides which are adequately described by the specification (i.e., SEQ ID NO: 1-5) have been disclosed as specifically binding to cardiac vasculature, the amount of additional experimentation required is undue.

Considering the nature of the invention, the level of the skill in the art required to make and/or use the claimed invention is deemed to be high.

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the full scope of the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention to its full scope. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 6, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,180,084 B1 (Ruoslahti et al.; hereafter "the '084 patent") in view of Sim (Angiogenesis 1998).

The instant claims are drawn to a chimeric molecule comprising a peptide angiogenic factor covalently linked to a targeting peptide that specifically binds to vascular endothelium (claim 1); wherein the angiogenic factor is angiostatin or endostatin (claim 5); wherein the molecule is a protein having a first subsequence comprising the angiogenic factor and a second

subsequence comprising the targeting peptide (claim 6); and pharmaceutical compositions comprising the chimeric molecule and a pharmaceutically acceptable carrier (claims 28 and 29).

The '084 patent teaches a chimeric molecule comprising an doxorubicin (an angiogenic factor) and a targeting peptide that specifically binds to the vascular endothelium of a tumor, wherein the angiogenic factor is covalently linked to the targeting peptide. For instance, the '084 patent teaches:

> "The present invention also provides for a method for directing a moiety to angiogenic vasculature of a tumor in a subject by administering to the subject a conjugate including a moiety linked to tumor homing molecule that exhibits specific binding to an NGR receptor, whereby the conjugate is directed to angiogenic vasculature of a tumor. " (See column 12, lines 62-67); and,
>
> "The invention also provides a method of inhibiting angiogenesis in a non-tumor tissue. The method includes a conjugate including a moiety linked to a homing molecule that exhibits specific binding to an NGR receptor, whereby the conjugate is directed to angiogenic vasculature of non-tumor tissue." (See column 13, lines 33-40); and,
>
> "A moiety can be a molecule such as a polypeptide or a nucleic acid to which a tumor homing molecule is grafted for the purpose of directing the polypeptide or nucleic acid to a selected tumor... For example, a peptide tumor homing molecule can be expressed as a fusion protein with a desired polypeptide such that the peptide targets the grafted polypeptide to a selected tumor." (See column 14, lines 30-40).

The '084 patent does not teach that the chimeric molecule comprises a peptide angiogenic factor such as angiostatin or endostatin.

Sim teaches that angiostatin and endostatin are endothelial cell-specific peptide inhibitors of angiogenesis and tumor growth. For example, Sim teaches, "Angiostatin and endostatin are potent inhibitors of angiogenesis." (See p. 37, abstract). Furthermore, Sim teaches, "Systemic administration of Angiostatin, but not intact plasminogen potently blocks neovascularization and growth of metastases *in vivo*." (See p. 41, last paragraph); and, "Recombinant mouse Endostatin produces in E. coli and delivered as an s.c. suspension at 20mg/kg/day potently suppressed the

growth of LLC solid tumors and even demonstrated an almost complete regression of established primary tumors" (See p. 44, first paragraph).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the '084 patent and Sim to create the claimed chimeric molecule comprising a targeting peptide (such as one of the targeting peptides taught by the '084 patent) covalently linked to a peptide angiogenic factor, such as angiostatin or endostatin (as taught by Sim) with a reasonable expectation of success.

The motivation to combine the references to create claimed invention is provided by the '084 patent which teaches, "the skilled artisan will recognize that various other chemotherapeutic agents can also be linked to a tumor homing molecule to make a conjugate of the invention." (See column 15, lines 26-28). It is noted that Sim teaches that Angiostatin and Endostatin are peptide angiogenic factors that are also anticancer agents (as indicated above).

It is noted that amending the claims such that they are limited to the targeting peptides of SEQ ID NO: 1-5 wherein the peptides specifically bind to cardiac vascular endothelium (as indicate above) would obviate the rejections and the claims would be allowable.

Applicants attention is directed to the claims of US Patent 6,303,573 (previously cited), which although not prior art, is considered a reference of interest.

Miscellaneous

It is noted that the claims had previously been rejected under 35 USC 112, 1st paragraph (written description and enablement) for the reasons set forth in the Action mailed on 1/17/03. However, the rejection and subsequent response form Applicants (dated 6/23/03) does not address the issues raised in the instant rejections. Specifically, the rejection and response did not address the issues with respect to the targeting peptides their binding specificity.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
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